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Pharmacology of angiotensin II receptors in the kidney

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Pharmacology of angiotensin II receptors in the kidney. Within the kidney angiotensin II (Ang II) exerts potent effects on renal function. The intrarenal actions of Ang II include modulation of renal blood flow, glomerular filtration rate, tubular epithelial transport, renin release and cellular growth. The actions of Ang II on the kidney are mediated by specific intrarenal receptors which, based upon physical characteristics and the selective binding of non-peptide and peptide analogs may be divided into two main subtypes, termed AT_1 and AT_2. AT_1 receptors are present within the kidneys of all species and are located predominantly in the glomerulus, the renal tubules and the renal vasculature, including the afferent and efferent arterioles. Modulation of AT_1 receptors within the kidney has been shown to mediate essentially all of the known intrarenal effects of Ang II. AT_1 receptors and particularly AT_2 receptors are expressed in large numbers in fetal kidney where they may play a role in development and maturation. In some species, intrarenal AT_2 receptors disappear shortly after birth. In those species where AT_2 receptors are present in the adult kidney their role in the control of renal function has not yet been clearly defined.

Within the kidney angiotensin II (Ang II) exerts potent effects on renal function. The intrarenal actions of Ang II include modulation of renal blood flow, glomerular filtration rate, tubular epithelial transport, renin release and cellular growth. Ang II binding sites have been localized in the kidney using *in vitro* autoradiography and in many cases have been correlated to changes in physiological function [1–3]. Variations in structural activity requirements and differences in signal transduction and regulatory mechanisms in several of the intrarenal actions of Ang II have been noted over the years [3]. These observation have led to the suggestion that the actions of Ang II within the kidney are mediated by different receptor subtypes. The recent availability of new peptide and non-peptide ligands has allowed this hypothesis to be confirmed with the unambiguous characterization of at least two distinct Ang II receptor subtypes [4]. The pharmacology of Ang II receptors subtypes within the kidney are summarized in the following brief review.

Characteristics of Ang II receptor subtypes

Recently, two receptor subtypes having clearly different binding characteristics were described in aortic smooth muscle, uterus and adrenal cortex [5, 6]. These initial observations have since been confirmed in a large number of tissues including the kidney [7–10]. Ang II receptors having a high affinity for losartan but a low affinity for CGP 42112 and PD 123319 are termed AT_1; whereas, Ang II receptors with a high affinity for CGP 42112 and PD 123319 but a low affinity for losartan are termed AT_2 [11].

The distribution of AT_1 and AT_2 receptor subtypes is heterogeneous between tissues. Some tissues, for example the liver and vascular smooth muscle cells in culture, express only the AT_1 receptor [5, 8], whereas only the AT_2 receptor is expressed in cerebellum, ovary follicles or the human uterus [5, 12, 13]. In some tissues, of which the adrenal cortex and heart are examples, both the AT_1 and AT_2 receptor subtypes are expressed [5, 7].

Three major characteristics distinguish the AT_1 and AT_2 receptor subtypes. Firstly, sulfhydril reducing agents such as dithiothreitol decrease the binding affinity of Ang II for the AT_1 receptor, whereas they increase the affinity of Ang II for the AT_2 receptor [11]. Secondly, in contrast to the AT_1 receptor, the AT_2 receptor does not appear to be coupled to a classical G-protein [14]. Finally, the AT_1 receptor-Ang II complex is rapidly internalized within cells, whereas the complex of Ang II with the AT_2 receptor is not [15, 16].

Both the AT_1 and AT_2 receptor have been cloned and are members of the 7-transmembrane domain superfamily, but have only a 30 to 35% amino acid sequence identity [17–20]. It has been clearly established that the AT_1 receptor is coupled to phospholipase C, adenylate cyclase and voltage-dependent calcium channels [21]. In contrast, the coupling mechanism of the AT_2 receptor has not yet been clearly defined, although evidence is accumulating to suggest linkage to a protein tyrosine phosphatase [14, 20].

Ang II receptor subtypes in the kidney

Autoradiography coupled with competitive binding studies have been used to characterize the distribution of Ang II receptor subtypes in renal tissue. Using these techniques, the distribution of AT_1 and AT_2 receptor subtypes within the kidney has been shown to be species dependent. For example, in the rat and rabbit kidney Ang II receptors are essentially of the AT_1 subtype [10, 22–24] while both AT_1 and AT_2 receptors are present within the kidney of the opossum and of primates including humans [23–26]. The distribution of renal Ang II receptors has been most extensively studied in the rat where the AT_1 receptor subtype is predominantly located in the glomerulus, the renal tubules and the renal vasculature [27–29]; these observations have been confirmed using reverse transcriptase, polymerase chain reactions and *in situ* hybridization [30–32]. In these latter studies, large signals for the AT_1 receptor were detected in the glomerulus, renal papilla, proximal convoluted tubule, proximal straight tubule, cortical collecting duct and the renal vascular system. Smaller signals for the AT_1 receptor have also been detected in medullary thick ascending limb, outer collecting duct and the

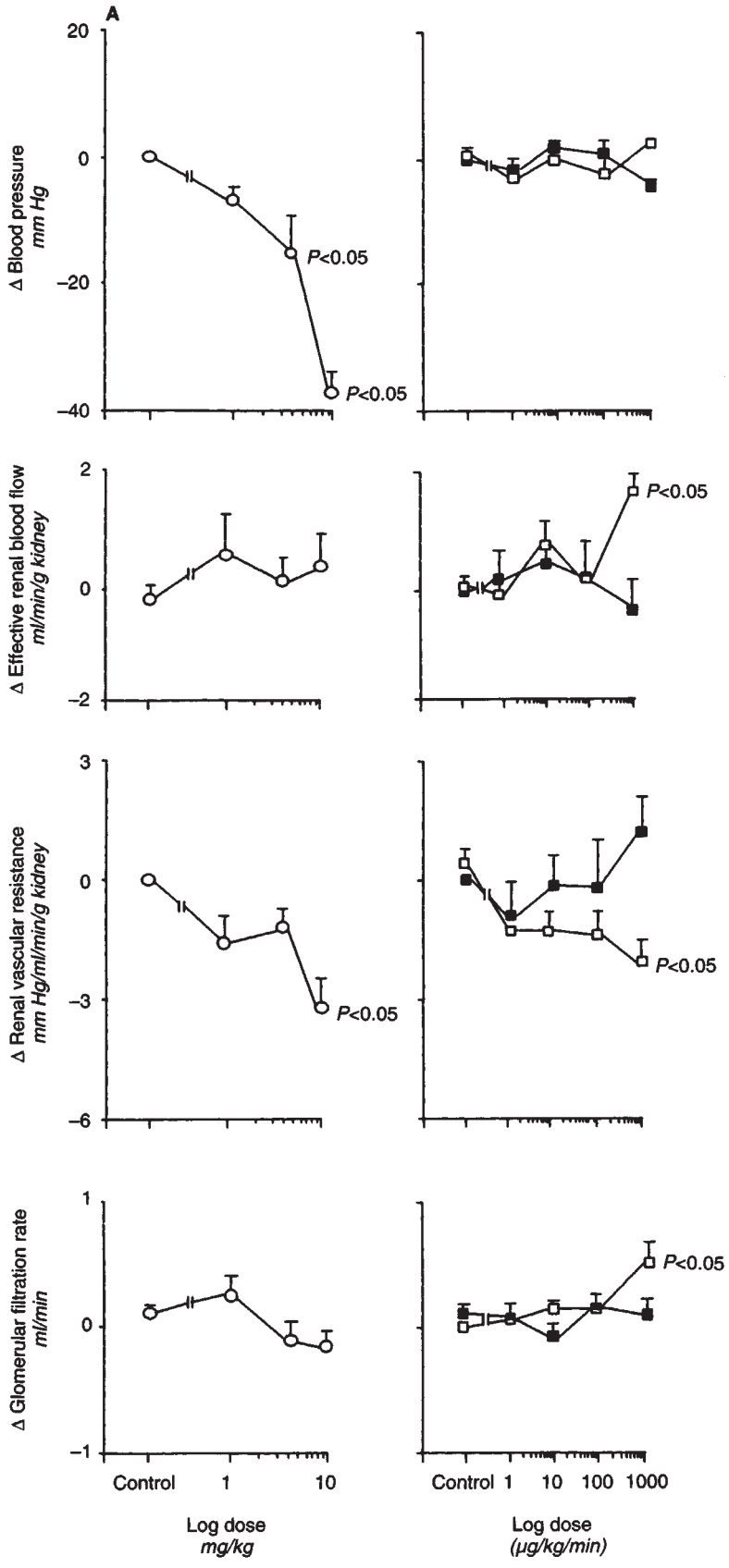

Fig. 1. *Effect of PD 123319 (■) and CGP 42112B (□) in comparison to losartan (○) on parameters of renal function in the sodium-depleted anesthetized rat.* The results represent the changes in each parameter of renal function produced by CGP 42112B, PD 123319 and losartan relative to baseline values. Statistics compare the changes in each parameter at each dose of drug relative to control values. The methodology and detailed results of these experiments have been previously described [54]. Reprinted with permission from the *European Journal of Pharmacology* [54].

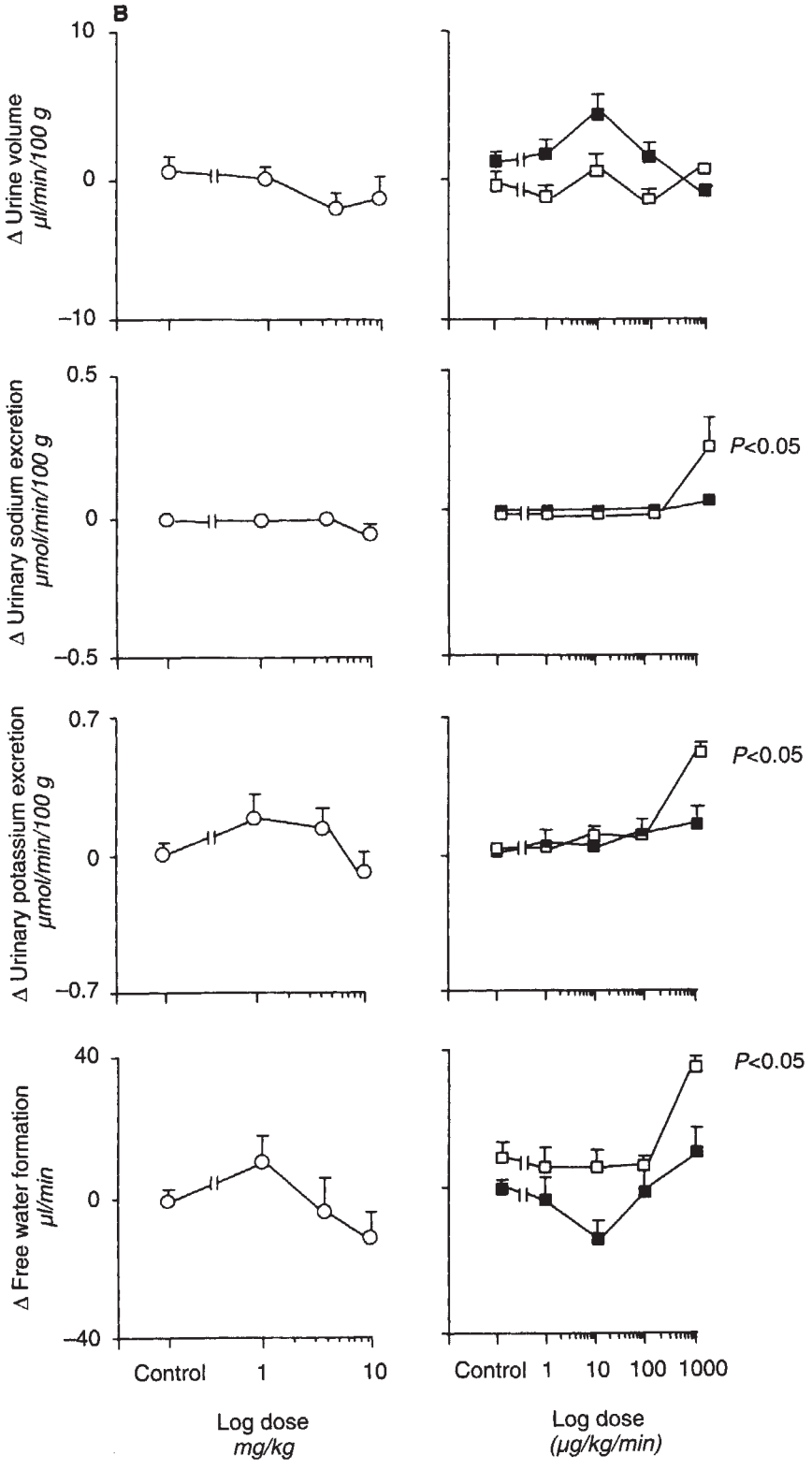

Fig. 1. *Continued.*

inner medullary collecting duct. Within the glomerulus, AT_1 mRNA localizes in mesangial areas, predominantly at the vascular pole and on the terminal portion of the afferent arteriole. In contrast, intense staining in all small arteries and arterioles, including both afferent and efferent arterioles has been observed using polyclonal antisera raised against a peptide sequence of the rat AT_1 receptor [33].

In agreement with conclusions derived from autoradiography

and receptor binding studies, AT_2 mRNA has not been detected by Northern blot analysis in the rat kidney [20]. However, in the rabbit the fibrous sheath around the kidney contains an exclusive population of AT_2 receptors [34]. In contrast to the rat and the rabbit, the AT_2 receptor subtype has been demonstrated in the renal cortex of the rhesus monkey on the intrarenal vasculature and on the juxtaglomerular apparatus [23]. In human kidney, the AT_2 receptor subtype is clearly present in large preglomerular vessels of the renal cortex and in the tubulointerstitium [26, 28].

Heterogeneity of renal Ang II receptor subtypes

Only a single gene encoding for the AT_1 receptor is expressed in human kidney [35, 36]. However, in rat kidney, as well as other tissues from this species, two clones encoding for different AT_1 receptor subtypes have been identified from genomic libraries [37]. These AT_1 receptor clones termed AT_{1A} and AT_{1B} have over 90% identity but differ in their amino acid sequence, primarily in the last intracellular loop of the receptor. Both receptor subtypes have essentially similar binding signatures and are pharmacologically indistinguishable from each other [38]. AT_{1A} and AT_{1B} more accurately describe isoforms rather than distinct subtypes of the Ang II receptor. The distribution of AT_{1A} and AT_{1B} receptor isoforms within the kidney have not been extensively studied although the AT_{1A} receptor, which is expressed predominantly in vascular smooth muscle, is most abundant in the glomerular mesangial area, the vascular component of the juxtaglomerular apparatus and the terminal portion of the afferent arteriole [31].

Receptor binding studies have also suggested the existence of two AT_1 receptor subpopulations in cultured rat mesangial cells [39]. One subpopulation, which has been termed AT_{1A}, represents 86% of the total number of binding sites and has a high affinity for losartan but a low affinity for CGP 42112 and PD123319. This receptor subtype thus resembles the AT_{1A} isoform described determined using molecular biology techniques and reported above. The remaining 14% of binding sites which have unfortunately been termed AT_{1B} have a 100-fold lower affinity for losartan and a 10'000-fold higher affinity for PD 123319 [39]. This latter subtype, despite its high affinity for PD 123319, differs from the typical AT_2 receptor subtype in having a low affinity for CGP 42112B and being coupled to a G-protein. Furthermore, since the AT_{1B} receptor subtype described by receptor binding methodology has remarkably different binding properties to the AT_{1B} receptor subtype described by molecular biology techniques they must be structurally distinct. The description of subgroups of Ang II receptors within the kidney which are clearly different but with similar labeling is confusing and requires standardization.

All AT_1 subtypes in the kidney are sensitive to GTP analogues and pertussis toxin and are linked to IP_3 generation, calcium mobilization and adenylate cyclase inhibition [10, 28, 39, 40]. Mesangial AT_{1A} receptors appear to mediate Ang II induced protein synthesis [41].

Binding studies performed with radioactive losartan in isolated rat glomeruli have demonstrated that in addition to labeling the AT_1 binding site, losartan may also recognize an additional receptor with characteristics different from known AT_1 or AT_2 receptors [29]. The significance of this observation is unclear at the present time.

Renal Ang II receptors during development

Within the kidney as well as in other tissues, both AT_1 and AT_2 receptors are developmentally regulated [9, 42]. The AT_2 receptor subtype predominates in tissues of the developing rat and human fetus, where they have a predominantly glomerular and medullary distribution [43, 44]. Although less numerous, AT_1 receptors are also present in the developing rat kidney. With increasing development AT_2 receptors disappear and the AT_1 receptor increases in number to become, at least in rat kidney, the predominant receptor subtype. Since all components of the renin-angiotensin system are present within the developing fetal/placental unit and Ang II plays a role in cell growth it has been suggested that Ang II acting through AT_2 receptors and perhaps also AT_1 receptors contribute to the growth and development of the immature kidney. This hypothesis is supported by the recent observation that treatment of fetal rats with either an angiotensin converting enzyme inhibitors or an AT_1 receptor antagonists leads to abnormalities of renal growth and to persistent defects in renal function in the adult animal [45].

Changes in renal function mediated by Ang II receptors

AT_1 receptors

Consistent with the intrarenal distribution described above, AT_1 receptors have been shown to mediate essentially all of the known effects of Ang II on kidney function [46–50]. The intrarenal actions of Ang II mediated by AT_1 receptors include vasoconstriction, alterations in glomerular hemodynamics and tubular reabsorption. AT_1 receptors present upon juxtaglomerular apparatus also mediate the negative feedback of Ang II on renin release and renal cell growth [23, 51].

AT_2 receptors

In contrast to the wealth of knowledge concerning the functional role of intrarenal Ang II receptors, little is known concerning the actions of Ang II mediated through the AT_2 receptor. There have been several reports suggesting that AT_2 ligands can affect renal function. For example, the AT_2 receptor ligands PD 123177 and PD 123319 have been shown to antagonize the renal vasoconstrictor response to exogenous Ang II and to induce an increase in urine volume and free water formation in the anesthetized dog [52]. Furthermore, in the conscious rat, PD 123177 has been shown to increase renal blood flow following experimental myocardial infarction and in the anaesthetized rat to increase glomerular filtration rate, urine volume, chloride and bicarbonate excretion [46, 53]. Since in the aforementioned studies, PD 123177 and PD 123319 were used at very high doses and in the majority of cases produced effects qualitative similar to AT_1 receptor antagonists, the possibility exists that PD 123177 and PD 123319 influence renal function by interacting with the AT_1 receptor or may exhibit non-specific properties. Both PD 123177 and PD 12319 are closely related compounds, and studies of renal function with other ligands selective for the AT_2 receptors have not yet been performed. Therefore it is unknown whether the renal actions of PD 123177 and PD 123319 are specific for this class of compounds or are a property of all ligands selective for the AT_2 receptor. Recently the role of AT_2 receptors in the control of kidney function has been reassessed using the highly selective AT_2 ligand CGP 42112 [54]. In these experiments, the renal actions of CGP 42112 in comparison to PD 123319 and

losartan were investigated in sodium-depleted anesthetized rats. The results in Figure 1 illustrate that PD 123319 at infusion rates of 1 to 1000 μg/kg/min had no effect on renal function, while CGP 42112 affected renal function only at an infusion rate of 1000 μg/kg/min. During these experiments the plasma levels of both compounds was monitored and compared to their known affinities for AT_1 and AT_2 receptors. Assuming the plasma concentrations of CGP 42112B and PD 123319 to be in equilibrium with those at the receptor level then at an infusion rates of 1 and 1000 μg/kg/min PD 123319 (plasma levels 70 nM and 25 μM, respectively) would be expected to interact essentially with an exclusive population of AT_2 receptors. At doses between 1 and 100 μg/kg/min, CGP 42112 (plasma levels of 14 and 700 nM, respectively) would be expected to bind to AT_2 receptors but at 1000 μg/kg/min (plasma levels 2.2 μM) to bind to 80% of the available AT_1 population. These results therefore suggest that AT_2 receptors are not involved in the control of renal function, at least in the anesthetized rat. It remains to be determined whether this is also the case in other species.

Summary

The actions of Ang II are mediated by at least two specific subtypes of receptor termed AT_1 and AT_2. The presence or ratio of AT_1 to AT_2 receptors within the kidney varies between species. In man only one form of the AT_1 receptor subtype is expressed whereas in the rat at least three closely related isoforms are expressed. The AT_1 receptor mediates essentially all of the known effects of Ang II on the kidney. Both the AT_1 receptor and particularly the AT_2 receptor are expressed in large numbers in the fetal kidney where they may play a role in growth and differentiation. In some species AT_2 receptors disappear from the kidney shortly after birth. In those species where they remain their role in the control of renal function has not been clearly defined. Additional work is needed to define the properties, intracellular mediators and pharmacological characteristics of intrarenal Ang II receptors.

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